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=> d his

     (FILE 'HOME' ENTERED AT 08:38:57 ON 09 MAR 2004)
               SET COST OFF

     FILE 'HCAPLUS' ENTERED AT 08:39:07 ON 09 MAR 2004
L1             0 S HB12605 OR HB12606 OR HB12607 OR HB12608 OR HB12609 OR HB1261
L2             0 S HB()(12605 OR 12606 OR 12607 OR 12608 OR 12609 OR 12610)
L3             0 S HB()12()(605 OR 606 OR 607 OR 608 OR 609 OR 610)
L4             0 S ATCC(L)12()(605 OR 606 OR 607 OR 608 OR 609 OR 610)
L5             0 S ATCC(L)(12605 OR 12606 OR 12607 OR 12608 OR 12609 OR 12610)
L6            32 S 12605 OR 12606 OR 12607 OR 12608 OR 12609 OR 12610
L7             0 S L6 AND (CDR OR CCR OR CCR5)
L8             0 S L6 AND ?CHEMOKIN?
L9             0 S L6 AND (MAB OR MONOCLON? OR ANTIBOD?)
L10          281 S PA8 OR PA9 OR PA10 OR PA11 OR PA12 OR PA14
L11          629 S PA()(8 OR 9 OR 10 OR 11 OR 12 OR 14)
L12          896 S L10,L11
L13            4 S L12 AND (CDR OR CCR OR CCR5)
L14            4 S L12 AND ?CHEMOKIN?
L15            4 S L13,L14
                 E OLSON W/AU
L16           19 S E3,E7,E8
                 E OLSON WILL/AU
L17           69 S E5,E10
                 E MADDON P/AU
L18           84 S E3-E8
                 E PROGENIC/PA,CS
L19           52 S E5-E16
                 E PROGEN/PA,CS
L20            3 S E44-E49
L21            4 S L12 AND L16-L20
L22            4 S L15,L21
L23          258 S PRO()(8 OR 80 OR 9 OR 90 OR 10 OR 100 OR 11 OR 110 OR 12 OR 1
L24            6 S L23 AND (CDR OR CCR OR CCR5)
L25            6 S L23 AND ?CHEMOKIN?
L26            6 S L24,L25
L27            5 S L26 NOT L22
                 SEL DN AN 1
L28            4 S L27 NOT E1-E3
L29            8 S L22,L28 AND L1-L28
                 E WO99-US30345/AP,PRN
L30            1 S E3,E4
                 SEL RN

     FILE 'REGISTRY' ENTERED AT 08:51:33 ON 09 MAR 2004
L31            1 S E1

     FILE 'HCAPLUS' ENTERED AT 08:51:55 ON 09 MAR 2004
L32            8 S L29,L30

=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 08:52:09 ON 09 MAR 2004
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FILE COVERS 1907 - 9 Mar 2004 VOL 140 ISS 11
FILE LAST UPDATED: 8 Mar 2004 (20040308/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d l32 all tot

L32 ANSWER 1 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:246838 HCAPLUS
DN 138:236783
ED Entered STN: 31 Mar 2003
TI The **CCR5** and CXCR4 coreceptors are both used by human immunodeficiency virus type 1 primary isolates from subtype C
AU Cilliers, Tonie; Nhlapo, Jabulani; Coetzer, Mia; Orlovic, Dragana; Ketas, Thomas; **Olson, William C.**; Moore, John P.; Trkola, Alexandra; Morris, Lynn
CS AIDS Virus Research Unit, National Institute for Communicable Diseases, Johannesburg, 2131, S. Afr.
SO Journal of Virology (2003), 77(7), 4449-4456
CODEN: JOVIAM; ISSN: 0022-538X
PB American Society for Microbiology
DT Journal
LA English
CC 15-8 (Immunochemistry)
AB Human immunodeficiency virus type 1 (HIV-1) subtype C viruses with different coreceptor usage profiles were isolated from 29 South African patients with advanced AIDS. All 24 R5 isolates were inhibited by the **CCR5**-specific agents, **PRO 140** and RANTES, while the two X4 viruses and the three R5X4 viruses were sensitive to the CXCR4-specific inhibitor, AMD3100. The five X4 or R5X4 viruses were all able to replicate in peripheral blood mononuclear cells that did not express **CCR5**. When tested using coreceptor-transfected cell lines, one R5 virus was also able to use CXCR6, and another R5X4 virus could use CCR3, BOB/GPR15, and CXCR6. The R5X4 and X4 viruses contained more-diverse V3 loop sequences, with a higher overall pos. charge, than the R5 viruses. Hence, some HIV-1 subtype C viruses are able to use **CCR5**, CXCR4, or both CXCR4 and **CCR5** for entry, and they are sensitive to specific inhibitors of entry via these coreceptors. These observations are relevant to understanding the rapid spread of HIV-1 subtype C in the developing world and to the design of intervention and treatment strategies.
ST HIV1 subtype C **CCR5** CXCR4 coreceptor T lymphocyte
IT **Chemokine** receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**CCR5**; HIV-1 subtype C can use both **CCR5** and CXCR4 coreceptors)
IT **Chemokine** receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(CXCR4; HIV-1 subtype C can use both **CCR5** and CXCR4 coreceptors)
IT AIDS (disease)
Human
Human immunodeficiency virus 1
Protein sequences
(HIV-1 subtype C can use both **CCR5** and CXCR4 coreceptors)
IT Envelope proteins

RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(HIV-1 subtype C can use both **CCR5** and CXCR4 coreceptors)

IT CD4-positive T cell
(disease, infection; HIV-1 subtype C can use both **CCR5** and CXCR4 coreceptors)

IT DNA sequences
Viral RNA sequences
(for envelope protein V3 loop fragments of human immunodeficiency virus)

IT 502130-81-6
RL: ADV (Adverse effect, including toxicity); PRP (Properties); BIOL (Biological study)
(nucleotide sequence; HIV-1 subtype C can use both **CCR5** and CXCR4 coreceptors)

IT 502130-83-8 502130-85-0 502130-87-2 502130-89-4 502130-91-8
502130-93-0 502130-95-2 502130-97-4 502130-99-6 502131-01-3
502131-05-7 502131-07-9 502131-09-1
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(nucleotide sequence; HIV-1 subtype C can use both **CCR5** and CXCR4 coreceptors)

RE.CNT 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L32 ANSWER 2 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:174230 HCAPLUS
DN 138:215262
ED Entered STN: 07 Mar 2003
TI Methods for inhibiting HIV-1 infection with antibody binding to **CCR5 chemokine** receptor or inhibiting HIV-1 fusion with cell positive for CD4 and **CCR5**
IN **Olson, William C.; Maddon, Paul J.**
PA USA
SO U.S. Pat. Appl. Publ., 50 pp.
CODEN: USXXCO
DT Patent
LA English
IC ICM A61K039-395
ICS A61K039-42
NCL 424144100; 424160100
CC 1-5 (Pharmacology)
Section cross-reference(s): 15
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2003044411	A1	20030306	US 2002-116797	20020405
PRAI US 2001-282380P	P	20010406		

AB This invention provides a method of reducing an HIV infected subject's HIV-1 viral load which comprises administering to the subject an effective viral load reducing amount of an antibody which (a) binds to a **CCR5 chemokine** receptor and (b) inhibits fusion of HIV-1 to a CD4+ **CCR5**+cell, so as to thereby reduce the subject's HIV-1 viral load to 50% or less of the subject's HIV-1 viral load prior to administering the antibody to the subject. A single 1 mg dose of anti-**CCR5** monoclonal antibody **PA14** gave potent antiviral activity in the hu-PBL-SCID mouse model of HIV-1 infection.
ST HIV1 infection inhibition antibody **CCR5 chemokine** receptor

IT **Chemokine** receptors
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(**CCR5**; inhibiting HIV-1 infection with antibody binding to **CCR5 chemokine** receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and **CCR5**)

IT Immunoglobulins
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PAC (Pharmacological activity); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(G1, monoclonal; inhibiting HIV-1 infection with antibody binding to **CCR5 chemokine** receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and **CCR5**)

IT Immunoglobulins
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(G2, fusion proteins with CD4, binding to gp120, synergistic inhibition of HIV-1 fusion using anti-**CCR5** and; inhibiting HIV-1 infection with antibody binding to **CCR5 chemokine** receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and **CCR5**)

IT CD4 (antigen)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cell pos. for **CCR5** and for; inhibiting HIV-1 infection with antibody binding to **CCR5 chemokine** receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and **CCR5**)

IT Hybridoma
(for monoclonal antibody production; inhibiting HIV-1 infection with antibody binding to **CCR5 chemokine** receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and **CCR5**)

IT Envelope proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gp120env, CD4-IgG2 binding to, synergistic inhibition of HIV-1 fusion using anti-**CCR5** and; inhibiting HIV-1 infection with antibody binding to **CCR5 chemokine** receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and **CCR5**)

IT Antibodies
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(humanized; inhibiting HIV-1 infection with antibody binding to **CCR5 chemokine** receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and **CCR5**)

IT AIDS (disease)
Anti-AIDS agents
Fusion, biological
Human
Human immunodeficiency virus 1
Infection
(inhibiting HIV-1 infection with antibody binding to **CCR5 chemokine** receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and **CCR5**)

IT Antibodies
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibiting HIV-1 infection with antibody binding to **CCR5 chemokine** receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and **CCR5**)

IT Drug delivery systems
(injections, i.m.; inhibiting HIV-1 infection with antibody binding to **CCR5 chemokine** receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and **CCR5**)

IT Drug delivery systems

(injections, i.p.; inhibiting HIV-1 infection with antibody binding to **CCR5 chemokine** receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and **CCR5**)

IT Drug delivery systems
(injections, i.v.; inhibiting HIV-1 infection with antibody binding to **CCR5 chemokine** receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and **CCR5**)

IT Drug delivery systems
(injections, s.c.; inhibiting HIV-1 infection with antibody binding to **CCR5 chemokine** receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and **CCR5**)

IT Antibodies
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PAC (Pharmacological activity); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(monoclonal; inhibiting HIV-1 infection with antibody binding to **CCR5 chemokine** receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and **CCR5**)

IT Drug delivery systems
(oral; inhibiting HIV-1 infection with antibody binding to **CCR5 chemokine** receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and **CCR5**)

IT RANTES (**chemokine**)
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synergistic inhibition of HIV-1 fusion using anti-**CCR5** monoclonal antibody and; inhibiting HIV-1 infection with antibody binding to **CCR5 chemokine** receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and **CCR5**)

IT Drug interactions
(synergistic; inhibiting HIV-1 infection with antibody binding to **CCR5 chemokine** receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and **CCR5**)

IT Drug delivery systems
(topical; inhibiting HIV-1 infection with antibody binding to **CCR5 chemokine** receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and **CCR5**)

IT Fusion proteins (chimeric proteins)
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(with CD4 and anti-gp120 IgG2; inhibiting HIV-1 infection with antibody binding to **CCR5 chemokine** receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and **CCR5**)

IT 500750-90-3
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(amino acid sequences; inhibiting HIV-1 infection with antibody binding to **CCR5 chemokine** receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and **CCR5**)

IT 159519-65-0, T 20 Peptide
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(and CD4-IgG2 and anti-**CCR5** synergistic inhibition of env-mediated membrane fusion; inhibiting HIV-1 infection with antibody binding to **CCR5 chemokine** receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and **CCR5**)

IT 500753-56-0 500753-57-1
RL: PRP (Properties)
(unclaimed protein sequence; methods for inhibiting HIV-1 infection with antibody binding to **CCR5 chemokine** receptor or

inhibiting HIV-1 fusion with cell pos. for CD4 and **CCR5**)

IT 352430-58-1
RL: PRP (Properties)
(unclaimed sequence; methods for inhibiting HIV-1 infection with antibody binding to **CCR5 chemokine** receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and **CCR5**)

L32 ANSWER 3 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:98579 HCAPLUS
DN 138:186210
ED Entered STN: 09 Feb 2003
TI Human immunodeficiency virus type 1 attachment, coreceptor, and fusion inhibitors are active against both direct and trans infection of primary cells
AU Ketas, Thomas J.; Frank, Ines; Klasse, Per Johan; Sullivan, Brian M.; Gardner, Jason P.; Spenlehauer, Catherine; Nesin, Mirjana; **Olson, William C.**; Moore, John P.; Pope, Melissa
CS **Progenics Pharmaceuticals, Inc., Tarrytown, NY, 10591, USA**
SO Journal of Virology (2003), 77(4), 2762-2767
CODEN: JOVIAM; ISSN: 0022-538X
PB American Society for Microbiology
DT Journal
LA English
CC 15-8 (Immunochemistry)
AB Inhibitors of human immunodeficiency virus type 1 attachment (CD4-IgG subclass 2), **CCR5** usage (**PRO 140**), and fusion (T-20) were tested on diverse primary cell types that represent the major targets both for infection in vivo and for the inhibition of trans infection of target cells by virus bound to dendritic cells. Although minor cell-type-dependent differences in potency were observed, each inhibitor was active on each cell type and trans infection was similarly vulnerable to inhibition at each stage of the fusion cascade.
ST HIV1 adhesion leukocyte CD4 antigen **CCR5** receptor
IT **Chemokine** receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**CCR5**; human immunodeficiency virus type 1 attachment, coreceptor, and fusion inhibitors are active against both direct and trans infection of primary cells)
IT Immunoglobulins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(G2; human immunodeficiency virus type 1 attachment, coreceptor, and fusion inhibitors are active against both direct and trans infection of primary cells)
IT Adhesion, biological
Dendritic cell
Fusion, biological
Human
Human immunodeficiency virus 1
Macrophage
Mononuclear cell (leukocyte)
(human immunodeficiency virus type 1 attachment, coreceptor, and fusion inhibitors are active against both direct and trans infection of primary cells)
IT CD4 (antigen)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(human immunodeficiency virus type 1 attachment, coreceptor, and fusion inhibitors are active against both direct and trans infection of primary cells)
RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L32 ANSWER 4 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:153944 HCAPLUS
DN 136:293396
ED Entered STN: 28 Feb 2002
TI Identification of amino acid residues critical for LD78β, a variant of human macrophage inflammatory protein-1α, binding to **CCR5** and inhibition of R5 human immunodeficiency virus type 1 replication
AU Miyakawa, Toshikazu; Obaru, Kenshi; Maeda, Kenji; Harada, Shigeyoshi; Mitsuya, Hiroaki
CS Department of Internal Medicine II, Kumamoto University School of Medicine, Kumamoto, 860-0811, Japan
SO Journal of Biological Chemistry (2002), 277(7), 4649-4655
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
CC 15-8 (Immunochemistry)
AB In an attempt to determine which amino acid(s) of LD78β, a variant of human macrophage inflammatory protein-1α, plays a critical role in the interaction with **CCR5**, we generated six LD78β variants with an amino acid substituted to Ala at the NH2 terminus of LD78β. There was no significant difference in eliciting Ca2+ flux and chemotaxis among the variants with the exception of LD78βT9A showing a substantially reduced activity. The comparative order for human immunodeficiency virus

type 1 (HIV-1) replication inhibition was: LD78βP8A > LD78βD6A > LD78βWT, LD78βL3A > LD78βT7A, LD78βP2A > LD78βT9A. In binding inhibition assays of LD78β variants using 2D7 monoclonal antibody and 125I-labeled macrophage inflammatory protein-1α, the comparative order was: LD78βP8A, LD78βD6A > LD78βWT > LD78βL3A > LD78βT7A > LD78βT9A, LD78βP2A. The order for **CCR5** down-regulation induction was comparable to that for binding inhibition. The present data suggest that Pro-2, Asp-6, **Pro-8**, and Thr-9 are critical for LD78β binding to **CCR5** and HIV-1 replication inhibition, and that LD78β binding to **CCR5**, regardless of affinity, is sufficient for the initial signal transduction of LD78β, whereas the greater anti-HIV-1 activity requires the greater magnitude of binding. The data also suggest that LD78β variants with appropriate amino acid substitution(s) such as LD78βD6A and LD78βP8A may represent effective **chemokine**-based anti-HIV-1 therapeutics while preserving LD78β- **CCR5** interactions.

ST HIV replication inhibition macrophage inflammatory protein **CCR5**

IT **Chemokine** receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**CCR5**; identification of amino acid residues critical for LD78β, a variant of human macrophage inflammatory protein-1α, binding to **CCR5** and inhibition of R5 HIV-1 virus replication)

IT Human
Protein sequences
Signal transduction, biological
(identification of amino acid residues critical for LD78β, a variant of human macrophage inflammatory protein-1α, binding to **CCR5** and inhibition of R5 HIV-1 virus replication)

IT Transcriptional regulation
(repression; identification of amino acid residues critical for LD78β, a variant of human macrophage inflammatory protein-1α, binding to **CCR5** and inhibition of R5 HIV-1 virus replication)

IT Macrophage inflammatory protein 1α
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(variants; identification of amino acid residues critical for LD78β, a variant of human macrophage inflammatory protein-1α, binding to **CCR5** and inhibition of R5 HIV-1 virus replication)

RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L32 ANSWER 5 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:905720 HCAPLUS
DN 137:72329
ED Entered STN: 16 Dec 2001
TI **PRO-140** (Progenics)
AU Poli, Guido
CS Istituto Scientifico H San Raffaele, Milan, 20132, Italy
SO IDrugs (2001), 4(9), 1068-1071
CODEN: IDRUFN; ISSN: 1369-7056
PB Current Drugs Ltd.
DT Journal; General Review
LA English
CC 1-0 (Pharmacology)
Section cross-reference(s): 15
AB A review. **PRO-140**, a monoclonal antibody against the HIV coreceptor **CCR5**, is under investigation by Progenics and the Aaron Diamond AIDS Research Center (ADARC) as a potential treatment for HIV infection [211441], [286246], [286247]. Phase I/II trials were expected to commence during 2001 [395621], [409142], despite being initially planned for 2000 [322637], [361819], [365216], [375598], [408483]. In Jan. 1998, ADARC and Progenics reported that the HIV binding site on the **CCR5** coreceptor is distinct from beta-**chemokine** binding domains, which they claimed may allow for the development of therapeutics with fewer side effects [273391], [421256]. In vitro studies have shown **PRO-140** potently blocked all of 17 primary HIV isolates that use **CCR5** as a fusion coreceptor [342173]. In Oct. 2000, Progenics was awarded an SBIR grant to fund a 2-yr project exploring the breadth, potency and durability of **PRO-140** therapy in laboratory and animal models of HIV infection. This project was a collaboration between Progenics, Weill Medical College of Cornell University and the Scripps Research Institute [385982]. In May 1999, the company entered into an agreement with Protein Design Labs (PDL) for the humanization by PDL of **PRO-140** [325445]. In Nov. 1997, Progenics was awarded a $600,000 grant from the NIAID for the examination of new approaches to HIV vaccine design based on **CCR5** [268407].
ST review mAb **PRO 140** potential HIV antiviral drug
IT **Chemokine** receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(**CCR5**; IgG1 mAb **PRO-140**: potential HIV antiviral drug)
IT Immunoglobulins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(G1, monoclonal, **PRO-140**; IgG1 mAb **PRO-140**: potential HIV antiviral drug)
IT Antiviral agents
Human immunodeficiency virus 1
(IgG1 mAb **PRO-140**: potential HIV antiviral drug)
IT Cytokines
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antagonist; IgG1 mAb **PRO-140**: potential HIV antiviral drug)
IT 339183-09-4, **CCR5** antibody
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(IgG1 mAb **PRO-140**: potential HIV antiviral drug)
RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L32 ANSWER 6 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:15173 HCAPLUS
DN 134:192003
ED Entered STN: 08 Jan 2001
TI Potent, broad-spectrum inhibition of human immunodeficiency virus type 1 by the **CCR5** monoclonal antibody **PRO 140**
AU Trkola, Alexandra; Ketas, Thomas J.; Nagashima, Kirsten A.; Zhao, Lu; Cilliers, Tonie; Morris, Lynn; Moore, John P.; **Maddon, Paul J.**; **Olson, William C.**
CS The Aaron Diamond AIDS Research Center, NY, USA
SO Journal of Virology (2001), 75(2), 579-588
CODEN: JOVIAM; ISSN: 0022-538X
PB American Society for Microbiology
DT Journal
LA English
CC 15-3 (Immunochemistry)
AB **CCR5** serves as a requisite fusion coreceptor for clin. relevant strains of human immunodeficiency virus type 1 (HIV-1) and provides a promising target for antiviral therapy. However, no study to date has examined whether monoclonal antibodies, small mols., or other non-**chemokine** agents possess broad-spectrum activity against the major genetic subtypes of HIV-1. **PRO 140** (**PA14**) is an anti-**CCR5** monoclonal antibody that potently inhibits HIV-1 entry at concns. that do not affect **CCR5**'s **chemokine** receptor activity. In this study, **PRO 140** was tested against a panel of primary HIV-1 isolates selected for their genotypic and geog. diversity. In quant. assays of viral infectivity, **PRO 140** was compared with RANTES, a natural **CCR5** ligand that can inhibit HIV-1 entry by receptor down-regulation as well as receptor blockade. Despite their divergent mechanisms of action and binding epitopes on **CCR5**, low nanomolar concns. of both **PRO**

140 and RANTES inhibited infection of primary peripheral blood mononuclear cells (PBMC) by all **CCR5**-using (R5) viruses tested. This is consistent with there being a highly restricted pattern of **CCR5** usage by R5 viruses. In addition, a panel of 25 subtype C South African R5 viruses were broadly inhibited by **PRO 140**, RANTES, and TAK-779, although .apprx.30-fold-higher concns. of the last compound were required. Interestingly, significant inhibition of a dual-tropic subtype C virus was also observed Whereas **PRO 140** potently inhibited HIV-1 replication in both PBMC and primary macrophages, RANTES exhibited limited antiviral activity in macrophage cultures. Thus **CCR5**-targeting agents such as **PRO 140** can demonstrate potent and genetic-subtype-independent anti-HIV-1 activity.

ST immunodeficiency virus infection **CCR5** receptor monoclonal antibody

IT Immunoglobulins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(G1, monoclonal, **PRO 140**; monoclonal antibody to **CCR**-5 receptor inhibits infection and replication by heterologous human immunodeficiency virus strains)

IT Macrophage
(infection; monoclonal antibody to **CCR**-5 receptor inhibits infection and replication by heterologous human immunodeficiency virus strains)

IT Human immunodeficiency virus 1
Mononuclear cell (leukocyte)
(monoclonal antibody to **CCR**-5 receptor inhibits infection and replication by heterologous human immunodeficiency virus strains)

IT Anti-AIDS agents
(monoclonal antibody to **CCR**-5 receptor inhibits infection and replication by heterologous human immunodeficiency virus strains in relation to)

IT Infection
(viral; monoclonal antibody to **CCR**-5 receptor inhibits infection and replication by heterologous human immunodeficiency virus strains)

IT **Chemokine** receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(β **chemokine** receptor **CCR5**; monoclonal antibody to **CCR**-5 receptor inhibits infection and replication by heterologous human immunodeficiency virus strains)

RE.CNT 78 THERE ARE 78 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L32 ANSWER 7 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:420924 HCAPLUS
DN 133:57579

ED Entered STN: 23 Jun 2000
TI Synergistic inhibition of HIV-1 attachment and cell fusion
IN **Olson, William C.; Maddon, Paul J.**
PA **Progenics Pharmaceuticals, Inc., USA**
SO PCT Int. Appl., 68 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K
CC 15-3 (Immunochemistry)
Section cross-reference(s): 1
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000035409	A2	20000622	WO 1999-US30345	19991216 <--
WO 2000035409	A3	20000914		
W: AU, CA, JP, MX				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2355607	AA	20000622	CA 1999-2355607	19991216 <--
AU 2000021996	A1	20000703	AU 2000-21996	19991216 <--
EP 1144006	A2	20011017	EP 1999-966466	19991216 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRAI US 1998-112532P P 19981216
US 1998-212793 A 19981216
WO 1999-US30345 W 19991216 <--

AB The authors disclose the inhibition of envelope-mediated fusion and human immunodeficiency virus-1 infection by the application of at least two compds. which act synergistically. In one example, pairs of monoclonal antibodies directed against the HIV-1 co-receptor **CCR5** were synergistic in their inhibition of cellular binding by gp120/sCD4. In a second example, anti-**CCR5** monoclonal antibody **PA12** was synergistic with RANTES in blocking cell-cell fusion.

ST HIV cell fusion antibody **CCR5 chemokine** receptor; immunodeficiency virus attachment **CCR5** receptor antibody

IT Immunoglobulins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(G1, monoclonal; to **chemokine** receptors for synergistic inhibition of human immunodeficiency virus attachment and cell fusion)

IT Immunoglobulins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(G2, fusion products, with CD4; synergistic inhibition of attachment and cell fusion by human immunodeficiency virus by interference with envelope protein binding by)

IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(IGL; for antibody chain mediating synergistic inhibition of attachment and cell fusion by human immunodeficiency virus)

IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Igh; for antibody chain mediating synergistic inhibition of attachment and cell fusion by human immunodeficiency virus)

IT **Chemokines**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(SDF-1 (stromal-derived factor-1); for synergistic inhibition of attachment and cell fusion by human immunodeficiency virus)

IT RANTES (**chemokine**)
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(derivs.; for synergistic inhibition of attachment and cell fusion by human immunodeficiency virus)

IT Epitopes
(for anti-**CCR5** antibodies mediating synergistic inhibition of attachment and cell fusion by human immunodeficiency virus)

IT RNA
cDNA
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(for antibody chain mediating synergistic inhibition of attachment and cell fusion by human immunodeficiency virus)

IT Macrophage inflammatory protein 1α
Macrophage inflammatory protein 1β
RANTES (**chemokine**)
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(for synergistic inhibition of attachment and cell fusion by human immunodeficiency virus)

IT Immunoglobulins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fragments; for synergistic inhibition of attachment and cell fusion by human immunodeficiency virus)

IT **Chemokine** receptors
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(fusin; synergistic inhibition of attachment and cell fusion by human immunodeficiency virus with monoclonal antibodies to)

IT CD4 (antigen)
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fusion products, with IgG2; synergistic inhibition of attachment and cell fusion by human immunodeficiency virus by interference with envelope protein binding by)

IT Envelope proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(gp120env; synergistic inhibition of attachment and cell fusion by human immunodeficiency virus by interference with binding to)

IT Immunoglobulins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(heavy chains; for synergistic inhibition of attachment and cell fusion by human immunodeficiency virus)

IT Antibodies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(humanized; for synergistic inhibition of attachment and cell fusion by human immunodeficiency virus)

IT Immunoglobulins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(light chains; for synergistic inhibition of attachment and cell fusion by human immunodeficiency virus)

IT Anti-AIDS agents
(monoclonal antibodies to **chemokine** receptors for synergistic inhibition of human immunodeficiency virus attachment and cell fusion)

IT Antibodies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(monoclonal; to **chemokine** receptors for synergistic inhibition of human immunodeficiency virus attachment and cell fusion)

IT Human immunodeficiency virus 1
(synergistic inhibition of attachment and cell fusion by)
IT Cell adhesion
Cell fusion
(synergistic inhibition of attachment and cell fusion by human immunodeficiency virus)
IT CD4 (antigen)
Envelope proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(synergistic inhibition of attachment and cell fusion by human immunodeficiency virus by interference with binding to)
IT Infection
(viral; synergistic inhibition of attachment and cell fusion by human immunodeficiency virus)
IT **Chemokine** receptors
Chemokine receptors
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(β **chemokine** receptor **CCR5**; synergistic inhibition of attachment and cell fusion by human immunodeficiency virus with monoclonal antibodies to)
IT **Chemokines**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(β, receptor **CCR5**; synergistic inhibition of attachment and cell fusion by human immunodeficiency virus with monoclonal antibodies to)
IT 155148-31-5, AMD3100
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(for synergistic inhibition of attachment and cell fusion by human immunodeficiency virus)

L32 ANSWER 8 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:263464 HCAPLUS
DN 131:57557
ED Entered STN: 30 Apr 1999
TI Differential inhibition of human immunodeficiency virus type 1 fusion, gp120 binding, and CC-**chemokine** activity by monoclonal antibodies to **CCR5**
AU **Olson, William C.**; Rabut, Gwenael E. E.; Nagashima, Kirsten A.; Tran, Diep N. H.; Anselma, Deborah J.; Monard, Simon P.; Segal, Jeremy P.; Thompson, Daniah A. D.; Kajumo, Francis; Guo, Yong; Moore, John P.; **Maddon, Paul J.**; Dragic, Tatjana
CS Aaron Diamond AIDS Research Center, The Rockefeller University, New York, NY, 10016, USA
SO Journal of Virology (1999), 73(5), 4145-4155
CODEN: JOVIAM; ISSN: 0022-538X
PB American Society for Microbiology
DT Journal
LA English
CC 15-3 (Immunochemistry)
AB The CC-**chemokine** receptor **CCR5** mediates fusion and entry of the most commonly transmitted human immunodeficiency virus type 1 (HIV-1) strains. The authors have isolated 6 new anti-**CCR5** murine monoclonal antibodies (MAbs), designated **PA8**, **PA9**, **PA10**, **PA11**, **PA12**, and **PA14**. A panel of **CCR5** alanine point mutants was used to map the epitopes of these MAbs and the previously described MAb 2D7 to specific amino acid residues in the N terminus and/or second extracellular loop regions of **CCR5**. This structural information was correlated with the MAbs' abilities to inhibit (1) HIV-1 entry, (2) HIV-1 envelope glycoprotein-mediated membrane fusion, (3) gp120 binding to **CCR5**, and (4) CC-**chemokine** activity. Surprisingly, there was no correlation between the ability of a MAb to inhibit HIV-1 fusion-entry and

its ability to inhibit either the binding of a gp120-soluble CD4 complex to **CCR5** or CC-**chemokine** activity. MAbs **PA9**-**PA12**, whose epitopes include residues in the **CCR5** N terminus, strongly inhibited gp120 binding but only moderately inhibited HIV-1 fusion and entry and had no effect on RANTES-induced calcium mobilization. MAbs **PA14** and 2D7, the most potent inhibitors of HIV-1 entry and fusion, were less effective at inhibiting gp120 binding and were variably potent at inhibiting RANTES-induced signaling. With respect to inhibiting HIV-1 entry and fusion, **PA12** but not **PA14** was potently synergistic when used in combination with 2D7, RANTES, and CD4-IgG2, which inhibits HIV-1 attachment. The data support a model wherein HIV-1 entry occurs in 3 stages: receptor (CD4) binding, coreceptor (**CCR5**) binding, and coreceptor-mediated membrane fusion. These antibodies will be useful for further dissecting these events.

ST HIV gp120 monoclonal antibody **CCR5 chemokine** receptor

IT **Chemokines**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(C-C; epitope mapping of monoclonal antibodies to **chemokine** receptor **CCR5**)

IT Immunoglobulins
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(G1, monoclonal; differential inhibition of HIV-1 fusion, gp120 binding, and CC-**chemokine** activity by monoclonal antibodies to **CCR5** receptor)

IT Fusion, biological
Human immunodeficiency virus 1
(differential inhibition of HIV-1 fusion, gp120 binding, and CC-**chemokine** activity by monoclonal antibodies to **CCR5** receptor)

IT Envelope proteins
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(gp120env; differential inhibition of HIV-1 fusion, gp120 binding, and CC-**chemokine** activity by monoclonal antibodies to **CCR5** receptor)

IT Epitopes
(mapping; epitope mapping of monoclonal antibodies to **chemokine** receptor **CCR5**)

IT **Chemokine** receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(β **chemokine** receptor **CCR5**; differential inhibition of HIV-1 fusion, gp120 binding, and CC-**chemokine** activity by monoclonal antibodies to **CCR5** receptor)

IT 200803-28-7 200803-29-8 228120-60-3 228120-61-4
RL: PRP (Properties)
(epitope mapping of monoclonal antibodies to **chemokine** receptor **CCR5**)

RE.CNT 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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FILE 'HCAPLUS' ENTERED AT 08:57:37 ON 09 MAR 2004

FILE 'BIOSIS' ENTERED AT 08:57:37 ON 09 MAR 2004

=> d all 9-13

L44 ANSWER 9 OF 13 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 2004:48240 BIOSIS
DN PREV200400050360
TI Immunotoxicology of **PRO 140**: A humanized anti-CCR5 monoclonal antibody for HIV-1 therapy.
AU Gardner, J. [Reprint Author]; Cohen, M. [Reprint Author]; Rosenfield, S. I. [Reprint Author]; Nagashima, K. A. [Reprint Author]; **Maddon, P. J.** [Reprint Author]; **Olson, W. C.** [Reprint Author]
CS **Progenics Pharmaceuticals Inc., Tarrytown, NY, USA**
SO Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy, (2003) Vol. 43, pp. 320. print.
Meeting Info.: 43rd Annual Interscience Conference on Antimicrobial Agents and Chemotherapy. Chicago, IL, USA. September 14-17, 2003. American Society for Microbiology.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 21 Jan 2004
Last Updated on STN: 21 Jan 2004
AB Background: The chemokine receptor CCR5 is a requisite fusion coreceptor for primary HIV-1 isolates and provides a promising target for a new generation of antiretroviral agents. **PRO 140** is a humanized anti-CCR5 monoclonal antibody (mAb) that broadly and potently blocks CCR5-mediated HIV-1 entry without CCR5 antagonism, thus offering a distinct therapeutic profile compared to small-molecule CCR5 antagonists in development. Immunotoxicology is an emerging field that examines the potential impact of drugs on immune system function. Here we report the findings of immunotoxicology studies performed using **PRO 140** prior to initiation of Phase 1 clinical testing. Methods: **PRO 140** was tested in a battery of in vitro assays of immune system function mediated by chemokine and non-chemokine mechanisms, and the immunologic activity of **PRO 140** was compared with its antiviral activity. Results: At concentrations that provide complete control of HIV-1 replication (apprx4 mug/mL), **PRO 140** had no effect on CCR5 signaling in response to CC-chemokines. Similarly, at concentrations ranging to 100 mug/mL, **PRO 140** had no effect on lymphocyte proliferation in response to mitogenic and allogeneic stimulation. Consistent with its IgG4,kappa subtype, **PRO 140** did not demonstrate significant binding to cells that express high levels of FcgammaR1 (CD64) and other Fc receptors. Lastly, **PRO 140** did not mediate significant levels of antibody-dependent cellular cytotoxicity or complement-dependent lysis of CCR5-expressing target cells. Conclusions: **PRO 140** did not interfere with normal immune system function in vitro, consistent with its lack of CCR5 antagonism and Fc-mediated effector activity. As an immunologically silent inhibitor of CCR5-mediated HIV-1 entry, **PRO 140** may offer distinct tolerability and therapeutic profiles in man.
CC General biology - Symposia, transactions and proceedings 00520
Cytology - General 02502
Cytology - Animal 02506
Cytology - Human 02508
Biochemistry studies - General 10060
Biochemistry studies - Proteins, peptides and amino acids 10064
Pathology - Therapy 12512
Blood - Blood and lymph studies 15002
Blood - Blood cell studies 15004
Endocrine - General 17002
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
Toxicology - General and methods 22501

Virology - General and methods 33502
Immunology - General and methods 34502
Immunology - Immunopathology, tissue immunology 34508
Medical and clinical microbiology - Virology 36006
Chemotherapy - General, methods and metabolism 38502
Chemotherapy - Antiviral agents 38506

IT Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology; Immune System (Chemical Coordination and Homeostasis); Infection; Pharmacology; Toxicology

IT Parts, Structures, & Systems of Organisms
cells; immune system: immune system, functions; lymphocytes: blood and lymphatics, immune system

IT Diseases
HIV-1 infection: immune system disease, viral disease, drug therapy, human immunodeficiency virus 1 infection
HIV Infections (MeSH)

IT Diseases
viral infection: viral disease, drug therapy
Virus Diseases (MeSH)

IT Chemicals & Biochemicals
CCR5 chemokine receptor: antagonists, functions; IgG [immunoglobulin G]; **PRO 140**: antiinfective-drug, antiviral-drug, applications, clinical uses/effects, humanized anti-CCR5 monoclonal antibody; antibodies; chemokines; complement; proteins

IT Methods & Equipment
antiviral therapy: clinical techniques, therapeutic and prophylactic techniques

IT Miscellaneous Descriptors
drug development; immunotoxicology; therapeutics; viral entry: inhibition; viral replication: control

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human (common)
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

ORGN Classifier
Retroviridae 03305
Super Taxa
DNA and RNA Reverse Transcribing Viruses; Viruses; Microorganisms
Organism Name
HIV-1 (miscellaneous) [Human immunodeficiency virus 1 (species)]: pathogen
Taxa Notes
DNA and RNA Reverse Transcribing Viruses, Microorganisms, Viruses

ORGN Classifier
Viruses 03000
Super Taxa
Microorganisms
Organism Name
Virus (common): pathogen, inhibition studies
Taxa Notes
Microorganisms, Viruses

L44 ANSWER 10 OF 13 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 2003:287881 BIOSIS
DN PREV200300287881
TI The humanized anti-CCR5 antibody **PRO 140** effectively inhibits HIV-1 entry without inhibiting RANTES-induced calcium mobilization.

AU O'Hara, B. [Reprint Author]; Gardner, J. P. [Reprint Author]; Ketas, T. J. [Reprint Author]; Sullivan, B. M. [Reprint Author]; Rosenfield, S. I. [Reprint Author]; Nagashima, K. A. [Reprint Author]; **Maddon, P. J.** [Reprint Author]; **Olson, W. C.** [Reprint Author]
CS **Progenics Pharmaceuticals, Inc., Tarrytown, NY, USA**
SO Antiviral Research, (February 2003) Vol. 57, No. 3, pp. A53. print.
Meeting Info.: Sixteenth International Conference on Antiviral Research. Savannah, GA, USA. April 27-May 01, 2003.
ISSN: 0166-3542 (ISSN print).
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 19 Jun 2003
Last Updated on STN: 1 Aug 2003
CC General biology - Symposia, transactions and proceedings 00520
Cytology - Animal 02506
Biochemistry studies - Proteins, peptides and amino acids 10064
Biochemistry studies - Minerals 10069
Biophysics - Membrane phenomena 10508
Pathology - Therapy 12512
Pharmacology - General 22002
Virology - General and methods 33502
Immunology - General and methods 34502
Medical and clinical microbiology - Virology 36006
Chemotherapy - General, methods and metabolism 38502
Chemotherapy - Antiviral agents 38506
IT Major Concepts
Immune System (Chemical Coordination and Homeostasis); Infection; Pharmacology
IT Parts, Structures, & Systems of Organisms
dendritic cells: immune system
IT Chemicals & Biochemicals
CCR5; PR 140: antiinfective-drug, antiviral-drug; RANTES; calcium: mobilization
IT Miscellaneous Descriptors
HIV entry
ORGN Classifier
Retroviridae 03305
Super Taxa
DNA and RNA Reverse Transcribing Viruses; Viruses; Microorganisms
Organism Name
HIV-1 (miscellaneous) [Human immunodeficiency virus 1 (species)]: pathogen
Taxa Notes
DNA and RNA Reverse Transcribing Viruses, Microorganisms, Viruses
RN 14191-75-4 (PR 140)
7440-70-2 (calcium)

L44 ANSWER 11 OF 13 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 2003:347815 BIOSIS
DN PREV200300347815
TI Inhibition of HIV-1 entry without receptor antagonism by the humanized anti-CCR5 antibody **PRO 140.**
AU **Olson, W. C.** [Reprint Author]; Gardner, J. P. [Reprint Author]; Ketas, T. J. [Reprint Author]; Sullivan, B. M. [Reprint Author]; Rosenfield, S. I. [Reprint Author]; Nagashima, K. A. [Reprint Author]; Moore, J. P.; **Maddon, P. J.** [Reprint Author]
CS **Progenics Pharmaceuticals, Inc., Tarrytown, NY, USA**
SO Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy, (2002) Vol. 42, pp. 264. print.
Meeting Info.: 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy. San Diego, CA, USA. September 27-30, 2002. American Society for Microbiology.

DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 30 Jul 2003
Last Updated on STN: 30 Jul 2003
AB Background: CCR5 is a requisite fusion coreceptor for primary HIV-1 isolates and provides a promising target for a new generation of antiretroviral agents. **PRO 140** is an anti-CCR5 monoclonal antibody (mAb) that broadly and potently blocks R5 virus entry (Trkola et al., J. Virol. 75:579, 2001). The parent mouse antibody was recently humanized to support repeat dosing in man, and humanized **PRO 140** is entering Phase 1 clinical testing. Methods: Humanized **PRO 140** was comparatively evaluated for its breadth of antiviral activity and effects on human immune cells in vitro. The antiviral activity was examined using both whole-virus p24 assays and a novel fluorometric membrane fusion assay. The virologic studies examined a broad range of wild-type and drug-resistant HIV-1 isolates and diverse primary target cell types. Immunologic studies explored the mAb's effects on both chemokine and non-chemokine signaling pathways. Results: **PRO 140** was broadly active in blocking HIV-1 replication in diverse and clinically relevant primary target cells, such as T cells, macrophages, and dendritic cells (DCs). The median IC90 values for the different viruses and cell types clustered about 5 mug/mL. This agent was similarly effective in blocking infection of T cells by DC-associated virus in trans. Complete suppression of viral replication was obtained at **PRO 140** concentrations that had little or no effect on CC-chemokine signaling through CCR5 and other normal immunologic activities. Conclusions: Humanized **PRO 140** broadly and potently blocks HIV-1 entry through CCR5 without interfering with the receptor's normal activity. This unique and compelling therapeutic profile warrants advancement of humanized **PRO 140** into human clinical testing.
CC General biology - Symposia, transactions and proceedings 00520
Cytology - General 02502
Cytology - Animal 02506
Cytology - Human 02508
Biochemistry studies - Proteins, peptides and amino acids 10064
Biophysics - Membrane phenomena 10508
Pathology - General 12502
Pathology - Therapy 12512
Blood - Blood and lymph studies 15002
Blood - Blood cell studies 15004
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
Virology - General and methods 33502
Immunology - General and methods 34502
Medical and clinical microbiology - Virology 36006
Chemotherapy - Antiviral agents 38506
IT Major Concepts
Cell Biology; Human Medicine (Medical Sciences); Immune System (Chemical Coordination and Homeostasis); Infection; Pharmacology
IT Parts, Structures, & Systems of Organisms
T-cells: blood and lymphatics, immune system; dendritic cells: immune system; macrophage: blood and lymphatics, immune system
IT Diseases
viral infection: viral disease, drug therapy
Virus Diseases (MeSH)
IT Chemicals & Biochemicals
CCR5: requisite fusion coreceptor; **PRO 140** humanized anti-CCR5 antibody: biological effects, pharmacological effects; antibodies; monoclonal antibodies: uses; proteins
IT Methods & Equipment
antiviral therapy: clinical techniques, therapeutic and prophylactic

techniques; drug therapy: clinical techniques, therapeutic and prophylactic techniques
IT Miscellaneous Descriptors
new drug discovery; receptor antagonism; viral replication: suppression; virologic studies: results
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human (common): patient
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
ORGN Classifier
Retroviridae 03305
Super Taxa
DNA and RNA Reverse Transcribing Viruses; Viruses; Microorganisms
Organism Name
HIV-1 (miscellaneous) [Human immunodeficiency virus 1 (species)]: pathogen, host cell entry inhibition
Taxa Notes
DNA and RNA Reverse Transcribing Viruses, Microorganisms, Viruses
ORGN Classifier
Viruses 03000
Super Taxa
Microorganisms
Organism Name
virus (common): pathogen
Taxa Notes
Microorganisms, Viruses

L44 ANSWER 12 OF 13 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 2002:565842 BIOSIS
DN PREV200200565842
TI The HIV-1 entry inhibitor **PRO 140** potently and durably suppresses viral replication in vitro and in vivo.
AU **Olson, W. C.** [Reprint author]; Franti, M.; Ketas, T. J. [Reprint author]; Nagashima, K. A. [Reprint author]; **Maddon, P. J.** [Reprint author]; Burton, D. R. [Reprint author]; Moore, J. P.; Poignard, P.
CS **Progenics Pharmaceuticals, Inc., Tarrytown, NY, USA**
SO Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy, (2001) Vol. 41, pp. 240. print.
Meeting Info.: 41st Annual Meeting of the Interscience Conference on Antimicrobial Agents and Chemotherapy. Chicago, Illinois, USA. September 22-25, 2001.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 7 Nov 2002
Last Updated on STN: 7 Nov 2002
AB Background: CCR5 is a requisite fusion coreceptor for primary HIV-1 isolates and provides a promising target for antiviral therapy. **PRO 140** is an anti-CCR5 monoclonal antibody that inhibits HIV-1 entry at concentrations that do not affect CCR5's chemokine receptor activity, and **PRO 140** mediates genetic subtype-independent inhibition of HIV-1 replication in primary T cells and macrophages (Trkola et al., J. Virol. 75:579, 2001). However, to date no published study has compared the potency and durability of viral suppression mediated by CCR5-targeting agents in vitro and in vivo. Methods: Viral sensitivity to **PRO 140** following prolonged exposure to this agent was evaluated in PBMC culture in vitro and in a therapeutic animal model of HIV-1 infection (Poignard et al.

Immunity 10:431, 1999). The in vitro studies employed the R5 biological clone HIV-1Case C 1/85 and a p24 readout, whereas the in vivo studies employed SCID mice reconstituted with normal human PBMC and later infected with the R5 isolate HIV-1JR-CSF. Animals were treated with single and multiple intraperitoneal injections of **PRO 140** and monitored for plasma viral RNA (Amplicor assay). Results: In both single-dose and multi-dose settings in vivo, **PRO 140** potently and durably reduced viral loads to undetectable levels. In addition, viruses remained sensitive to **PRO 140** following prolonged periods of exposure both in vitro and in vivo. Conclusions: **PRO 140** demonstrated potent and sustained activity against primary viruses both in vitro and in a well-recognized animal model of HIV-1 infection. These findings underscore the therapeutic potential of CCR5-targeting agents in general and **PRO 140** in particular.

CC General biology - Symposia, transactions and proceedings 00520
Cytology - Animal 02506
Cytology - Human 02508
Biochemistry studies - Proteins, peptides and amino acids 10064
Biophysics - Membrane phenomena 10508
Pathology - Therapy 12512
Blood - Blood and lymph studies 15002
Blood - Blood cell studies 15004
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
Virology - Animal host viruses 33506
Immunology - General and methods 34502
Immunology - Immunopathology, tissue immunology 34508
Medical and clinical microbiology - Virology 36006

IT Major Concepts
Immune System (Chemical Coordination and Homeostasis); Infection; Pharmacology

IT Parts, Structures, & Systems of Organisms
PBMC: blood and lymphatics, immune system, peripheral blood mononuclear cell

IT Diseases
HIV-1 infection: immune system disease, viral disease, human immunodeficiency virus 1 infection
HIV Infections (MeSH)

IT Chemicals & Biochemicals
CCR5; **PRO 140**: anti-CCR5 monoclonal antibody, human immunodeficiency virus-1 entry inhibitor

IT Miscellaneous Descriptors
Meeting Abstract

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
SCID mouse [severe combined immunodeficiency mouse]: animal model
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

ORGN Classifier
Retroviridae 03305

Super Taxa
DNA and RNA Reverse Transcribing Viruses; Viruses; Microorganisms
Organism Name
HIV-1 [human immunodeficiency virus 1]: pathogen, replication, suppression
Taxa Notes
DNA and RNA Reverse Transcribing Viruses, Microorganisms, Viruses

L44 ANSWER 13 OF 13 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 2001:2603 BIOSIS
DN PREV200100002603
TI Potent, broad-spectrum inhibition of HIV-1 by the CCR5 antibody **PRO 140.**
AU **Olson, W. C.** [Reprint author]; Ketas, T. J. [Reprint author]; Nagashima, K. A. [Reprint author]; Zhao, L. [Reprint author]; **Maddon, P. J.** [Reprint author]; Moore, J. P.; Trkola, A.
CS **Progenics Pharmaceuticals, Inc., Tarrytown, NY, USA**
SO Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy, (2000) Vol. 40, pp. 283. print.
Meeting Info.: 40th Interscience Conference on Antimicrobial Agents and Chemotherapy. Toronto, Ontario, Canada. September 17-20, 2000. Interscience Conference on Antimicrobial Agents and Chemotherapy; American Society of Microbiology.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LA English
ED Entered STN: 21 Dec 2000
Last Updated on STN: 21 Dec 2000
CC Immunology - General and methods 34502
General biology - Symposia, transactions and proceedings 00520
Cytology - Animal 02506
Biochemistry studies - Proteins, peptides and amino acids 10064
Biophysics - Membrane phenomena 10508
Pathology - Therapy 12512
Blood - Blood and lymph studies 15002
Blood - Blood cell studies 15004
Pharmacology - General 22002
Virology - Animal host viruses 33506
Medical and clinical microbiology - Virology 36006
Chemotherapy - Antiviral agents 38506
IT Major Concepts
Immune System (Chemical Coordination and Homeostasis); Infection; Pharmacology
IT Parts, Structures, & Systems of Organisms
T cell: blood and lymphatics, immune system; macrophage: blood and lymphatics, immune system; peripheral blood mononuclear cells: blood and lymphatics, immune system
IT Chemicals & Biochemicals
CCR5; **PRO 140**: antiviral-drug, anti-CCR5 antibody; RANTES [regulation upon activation normal T cell expressed and secreted]
IT Methods & Equipment
antiviral therapy: therapeutic method
IT Miscellaneous Descriptors
Meeting Abstract; Meeting Poster
ORGN Classifier
Retroviridae 03305
Super Taxa
DNA and RNA Reverse Transcribing Viruses; Viruses; Microorganisms
Organism Name
HIV-1 [human immunodeficiency virus 1]: broad spectrum inhibition, pathogen, replication

Taxa Notes
DNA and RNA Reverse Transcribing Viruses, Microorganisms, Viruses

=> => d all tot

L48 ANSWER 1 OF 2 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 2003:563353 BIOSIS
DN PREV200300565245
TI The entry of entry inhibitors: A fusion of science and medicine.
AU Moore, John P.; Doms, Robert W. [Reprint Author]
CS Department of Pathology and Laboratory Medicine, University of Pennsylvania, 34th and Civic Center Boulevard, 806 Abramson, Philadelphia, PA, 19104, USA
jpm2003@pop.med.cornell.edu; doms@mail.med.upenn.edu
SO Proceedings of the National Academy of Sciences of the United States of America, (September 16 2003) Vol. 100, No. 19, pp. 10598-10602. print.
ISSN: 0027-8424 (ISSN print).
DT Article
LA English
ED Entered STN: 3 Dec 2003
Last Updated on STN: 3 Dec 2003
AB For HIV-1 to enter a cell, its envelope protein (Env) must sequentially engage CD4 and a **chemokine** coreceptor, triggering conformational changes in Env that ultimately lead to fusion between the viral and host cell membranes. Each step of the virus entry pathway is a potential target for novel antiviral agents termed entry inhibitors. A growing number of entry inhibitors are under clinical development, with one having already been licensed by the Food and Drug Administration. With the emergence of virus strains that are largely resistant to existing reverse transcriptase and protease inhibitors, the development of entry inhibitors comes at an opportune time. Nonetheless, because all entry inhibitors target in some manner the highly variable Env protein of HIV-1, there are likely to be challenges in their efficient application that are unique to this class of drugs. Env density, receptor expression levels, and differences in affinity and receptor presentation are all factors that could influence the clinical response to this promising class of new antiviral agents.
CC Biochemistry studies - Proteins, peptides and amino acids 10064
Biophysics - Membrane phenomena 10508
Pathology - Therapy 12512
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
Virology - General and methods 33502
Immunology - Immunopathology, tissue immunology 34508
Medical and clinical microbiology - Virology 36006
Chemotherapy - General, methods and metabolism 38502
Chemotherapy - Antiviral agents 38506
IT Major Concepts
Infection; Pharmacology
IT Diseases
HIV-1 infection: immune system disease, viral disease, drug therapy, human immunodeficiency virus 1 infection
HIV Infections (MeSH)
IT Chemicals & Biochemicals
AMD070: antiinfective-drug, antiviral-drug; AMD3100: antiinfective-drug, antiviral-drug; BMS-806: antiinfective-drug, antiviral-drug; **CCR5**; CD4; CXCR4; **PRO-140** : antiinfective-drug, antiviral-drug; PRO-542: antiinfective-drug, antiviral-drug; SCH-C: antiinfective-drug, antiviral-drug; SCH-D: antiinfective-drug, antiviral-drug; T20: antiinfective-drug, antiviral-drug; TNX-355: antiinfective-drug, antiviral-drug; UK-427857: antiinfective-drug, antiviral-drug; envelope protein

IT Miscellaneous Descriptors
FDA industry; drug development
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human (common): host
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
ORGN Classifier
Retroviridae 03305
Super Taxa
DNA and RNA Reverse Transcribing Viruses; Viruses; Microorganisms
Organism Name
HIV-1 (miscellaneous) [Human immunodeficiency virus 1 (species)]: pathogen
Taxa Notes
DNA and RNA Reverse Transcribing Viruses, Microorganisms, Viruses
RN 155148-31-5 (AMD3100)
339184-91-7 (CXCR4)
383198-58-1 (PRO-542)

L48 ANSWER 2 OF 2 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 2002:207314 BIOSIS
DN PREV200200207314
TI Identification of amino acid residues critical for LD78beta, a variant of human macrophage inflammatory protein-1alpha, binding to **CCR5** and inhibition of R5 human immunodeficiency virus type 1 replication.
AU Miyakawa, Toshikazu; Obaru, Kenshi; Maeda, Kenji; Harada, Shigeyoshi; Mitsuya, Hiroaki [Reprint author]
CS Dept. of Internal Medicine II, Kumamoto University School of Medicine, 1-1-1 Honjo, Kumamoto, 860-0811, Japan
hm21q@nih.gov
SO Journal of Biological Chemistry, (February 15, 2002) Vol. 277, No. 7, pp. 4649-4655. print.
CODEN: JBCHA3. ISSN: 0021-9258.
DT Article
LA English
ED Entered STN: 20 Mar 2002
Last Updated on STN: 20 Mar 2002
AB In an attempt to determine which amino acid(s) of LD78beta, a variant of human macrophage inflammatory protein-1alpha, plays a critical role in the interaction with **CCR5**, we generated six LD78beta variants with an amino acid substituted to Ala at the NH2 terminus of LD78beta. There was no significant difference in eliciting Ca2+ flux and chemotaxis among the variants with the exception of LD78betaT9A showing a substantially reduced activity. The comparative order for human immunodeficiency virus type 1 (HIV-1) replication inhibition was: LD78betaP8A > LD78betaD6A > LD78betaWT, LD78betaL3A > LD78betaT7A, LD78betaP2A > LD78betaT9A. In binding inhibition assays of LD78beta variants using 2D7 monoclonal antibody and 125I-labeled macrophage inflammatory protein-1alpha, the comparative order was: LD78betaP8A, LD78betaD6A > LD78betaWT > LD78betaL3A > LD78betaT7A > LD78betaT9A, LD78betaP2A. The order for **CCR5** down-regulation induction was comparable to that for binding inhibition. The present data suggest that Pro-2, Asp-6, **Pro-8**, and Thr-9 are critical for LD78beta binding to **CCR5** and HIV-1 replication inhibition, and that LD78beta binding to **CCR5**, regardless of affinity, is sufficient for the initial signal transduction of LD78beta, whereas the greater anti-HIV-1 activity requires the greater magnitude of binding. The data also suggest that LD78beta variants with appropriate amino acid substitution(s) such as LD78betaD6A and LD78betaP8A may represent effective **chemokine**-based anti-HIV-1 therapeutics

while preserving LD78beta-**CCR5** interactions.
CC Cytology - Human 02508
Biochemistry studies - General 10060
Biochemistry studies - Proteins, peptides and amino acids 10064
Biochemistry studies - Minerals 10069
Biophysics - Membrane phenomena 10508
Pathology - Therapy 12512
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
Virology - Animal host viruses 33506
Medical and clinical microbiology - Virology 36006
Chemotherapy - General, methods and metabolism 38502
Chemotherapy - Antiviral agents 38506
IT Major Concepts
Biochemistry and Molecular Biophysics; Infection; Methods and Techniques; Pharmacology
IT Chemicals & Biochemicals
2D7 monoclonal antibody: PharMingen; **CCR5**; LD78-beta: antiinfective-drug, antiviral-drug, amino acid substituted variants; amino acid residues; calcium (II) ion; iodine-125-labeled-macrophage inflammatory protein-1-alpha [iodine-125-labeled-MIP-1-alpha]: Amersham Biosciences, Inc.; macrophage inflammatory protein-1-alpha [MIP-1-alpha]: Peprotech, Inc.
IT Methods & Equipment
ARC-370M Gamma System: Aloka Technical Service Co. Ltd., laboratory equipment; Epics XL: Coulter, laboratory equipment; binding inhibition assays: Bioassays/Physiological Analysis, bioassay method
IT Miscellaneous Descriptors
chemotaxis; viral replication inhibition
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
CCR5-Molt4 cell line
human
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
ORGN Classifier
Retroviridae 03305
Super Taxa
DNA and RNA Reverse Transcribing Viruses; Viruses; Microorganisms
Organism Name
R5 human immunodeficiency virus type 1 [R5 HIV-1]: pathogen
Taxa Notes
DNA and RNA Reverse Transcribing Viruses, Microorganisms, Viruses
RN 14127-61-8 (calcium (II) ion)

=> => d his

(FILE 'HOME' ENTERED AT 08:38:57 ON 09 MAR 2004)
SET COST OFF

FILE 'HCAPLUS' ENTERED AT 08:39:07 ON 09 MAR 2004
L1 0 S HB12605 OR HB12606 OR HB12607 OR HB12608 OR HB12609 OR HB1261
L2 0 S HB()(12605 OR 12606 OR 12607 OR 12608 OR 12609 OR 12610)
L3 0 S HB()12()(605 OR 606 OR 607 OR 608 OR 609 OR 610)
L4 0 S ATCC(L)12()(605 OR 606 OR 607 OR 608 OR 609 OR 610)
L5 0 S ATCC(L)(12605 OR 12606 OR 12607 OR 12608 OR 12609 OR 12610)
L6 32 S 12605 OR 12606 OR 12607 OR 12608 OR 12609 OR 12610
L7 0 S L6 AND (CDR OR CCR OR CCR5)
L8 0 S L6 AND ?CHEMOKIN?

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L9            0 S L6 AND (MAB OR MONOCLON? OR ANTIBOD?)
L10         281 S PA8 OR PA9 OR PA10 OR PA11 OR PA12 OR PA14
L11         629 S PA()(8 OR 9 OR 10 OR 11 OR 12 OR 14)
L12         896 S L10,L11
L13           4 S L12 AND (CDR OR CCR OR CCR5)
L14           4 S L12 AND ?CHEMOKIN?
L15           4 S L13,L14
                E OLSON W/AU
L16          19 S E3,E7,E8
                E OLSON WILL/AU
L17          69 S E5,E10
                E MADDON P/AU
L18          84 S E3-E8
                E PROGENIC/PA,CS
L19          52 S E5-E16
                E PROGEN/PA,CS
L20           3 S E44-E49
L21           4 S L12 AND L16-L20
L22           4 S L15,L21
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L25           6 S L23 AND ?CHEMOKIN?
L26           6 S L24,L25
L27           5 S L26 NOT L22
                SEL DN AN 1
L28           4 S L27 NOT E1-E3
L29           8 S L22,L28 AND L1-L28
                E WO99-US30345/AP,PRN
L30           1 S E3,E4
                SEL RN

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L31           1 S E1

     FILE 'HCAPLUS' ENTERED AT 08:51:55 ON 09 MAR 2004
L32           8 S L29,L30

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                SEL RN 8

     FILE 'REGISTRY' ENTERED AT 08:52:55 ON 09 MAR 2004
L33           4 S E2-E5

     FILE 'BIOSIS' ENTERED AT 08:53:19 ON 09 MAR 2004
                E OLSSON W/AU
                E OLSON W/AU
L34          75 S E3,E7,E8
                E OLSON WILL/AU
L35          49 S E4,E6
                E MADDON P/AU
L36          86 S E3-E6
                E PROGEN/CS
L37          50 S E38 OR PROGENICS?/CS
L38         189 S L34-L37
L39         359 S L23
L40         390 S L10 OR L11
L41           0 S L1-L5
L42          28 S L6
L43           9 S L38 AND L39-L42

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